

On the use of 1,3-dienylboronates in Diels–Alder reactions. Part I: a strategy towards the synthesis of clerodin

Pierre-Yves Renard, Jean-Yves Lallemand*

Laboratoire de synthèse organique, École polytechnique, 91128 Palaiseau, France

(Received 14 September 1995; accepted 4 December 1995)

Summary — A construction of the pivotal C₉–C₁₁ junction between the two subunits of clerodin **1** is proposed via a stereocontrolled tandem Diels–Alder/allylboration process. 1,3-Dienylboronate **8** was formed by hydroboration of enyne **7** and underwent Diels–Alder cycloaddition with methyl acrylate. The resulting allylboronate was then directly condensed with 4-(benzyloxy)butanal **12** yielding cyclohexene **14a** (63% from catecholborane), which displayed the desired C₉–C₁₁ stereochemistry. The protected alcohol **19a** was then converted via a smooth oxidative decarboxylation process into cyclohexenone **21**, which is a key intermediate in the total synthesis of clerodin.

1,3-dienylboronate / Diels–Alder / allylboration / clerodin / oxidative decarboxylation

Résumé — Utilisation des 1,3-diénylboronates dans les réactions de Diels–Alder. I. Une stratégie pour la synthèse de la clérodine. Cet article présente une construction de la liaison clef C₉–C₁₁ entre les deux sous parties de la clérodine **1**. La séquence réactionnelle est constituée d'une réaction de Diels–Alder entre un 1,3-diénylboronate et un diénophile activé, immédiatement suivie in situ d'une homoaldolisation. Une décarboxylation oxydante permet alors d'obtenir un intermédiaire avancé de la synthèse de la clérodine en seulement trois étapes au total.

1,3-diénylboronate / Diels–Alder / allylboration / clérodine / décarboxylation oxydante

Clerodin **1**, like many members of the clerodane family, displays interesting anti-appetite activity [1]. This challenging structure has attracted the attention of many synthetic chemists, but no total synthesis has been achieved so far. We previously described the condensation of the furo[2,3-*b*]furan moiety of clerodin from the model intermediate **4** [2a], and the construction of the *trans*-decalinic moiety from the cyclohexenone **5** [2b]. The pivotal point in our approach to clerodin [3] is the enantio- and stereocontrolled formation of the C₉–C₁₁ bond. We have now addressed this issue and have devoted our efforts to the synthesis of models such as **2** and **3** (scheme 1).

Recently, a stereoselective tandem reaction was described by Vaultier and Hoffmann [4] involving Diels–Alder reaction of a 1,3-dienylboronate followed by the condensation with an aldehyde. On the basis of this reaction, we propose a retrosynthetic approach for the construction of **2** and **3** (scheme 2).

Results and discussion

Tandem Diels–Alder/condensation reaction

We first tested this reaction with methyl acrylate as the dienophile. Diene **8** was easily prepared through direct and quantitative hydroboration of enyne **7** with

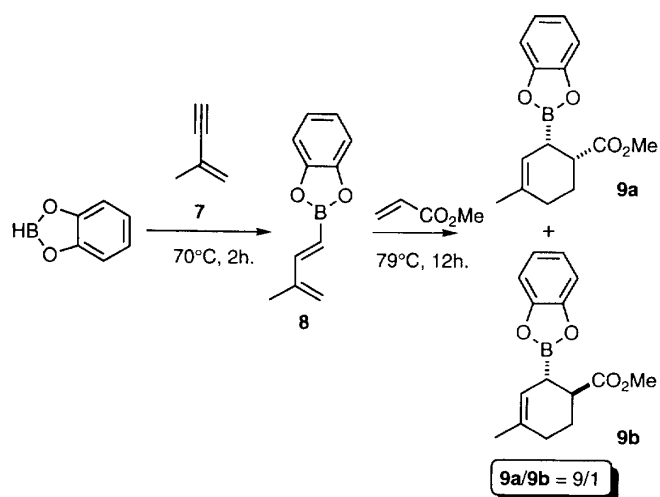
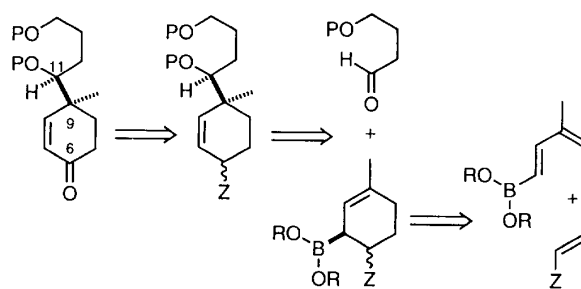
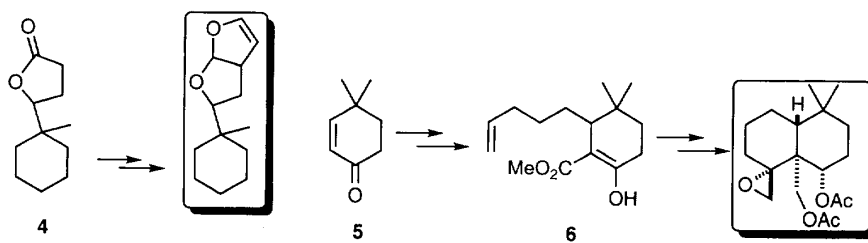
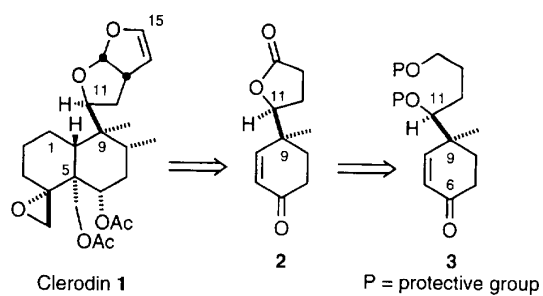
catecholborane. The Diels–Alder reaction of **8** with methyl acrylate proved to be fully regioselective and quite endoselective when performed without solvent, at 79 °C. Allylboronates **9a** and **9b** were then obtained in a 9:1 ratio (scheme 3), whereas a similar reaction, using toluene as solvent at 100 °C, showed almost no *endo/exo* selectivity (1.8:1) [4a].

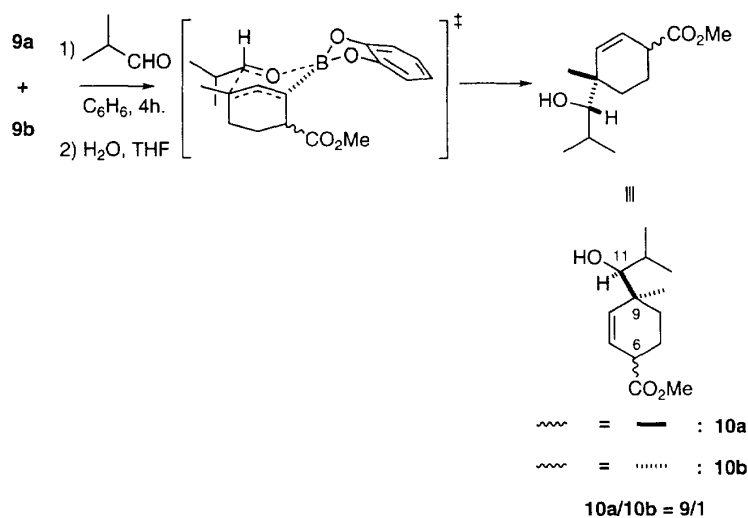
The condensation of isobutyraldehyde onto the crude allylic boronates **9a,b** (9:1 mixture) allowed us to synthesize cyclohexenes **10a,b** with a global yield of 76% from catecholborane. The allylboration is assumed to occur through a Zimmerman–Traxler-type chair-like transition state with the bulky isopropyl group of the aldehyde being shifted to the pseudo-equatorial position. Compounds **10a** and **10b** were also obtained as a 9:1 mixture, which supports the idea that the diastereoselectivity of the allylboration reaction is fully controlled by this kind of transition state (scheme 4).

When it was treated with *t*-BuOK/H₂O (4:1) [5] in Et₂O, the mixture of cyclohexenes **10a,b** afforded a single bicyclic compound **11** in 86% yield in which epimerization at carbon 6 had occurred. 2D ¹H COSY and NOESY experiments on **11** confirmed the C₉–C₁₁ stereochemistry for cyclohexenes **10a,b** (scheme 5).

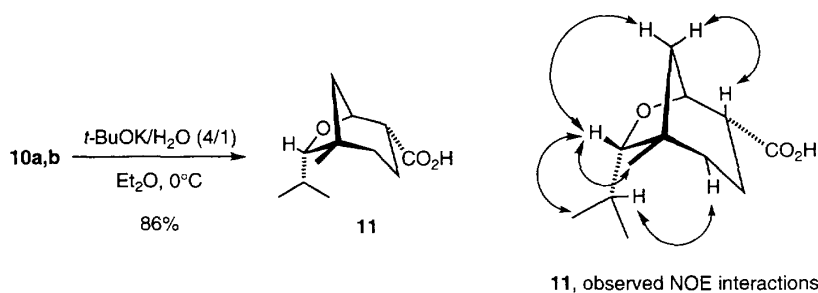
The mixture of allylboronates **9a** and **9b** was also reacted with aldehydes **12** and **13** bearing additional functionalities. This yielded cyclohexenes **14a,b** and

* Correspondence and reprints





Scheme 4



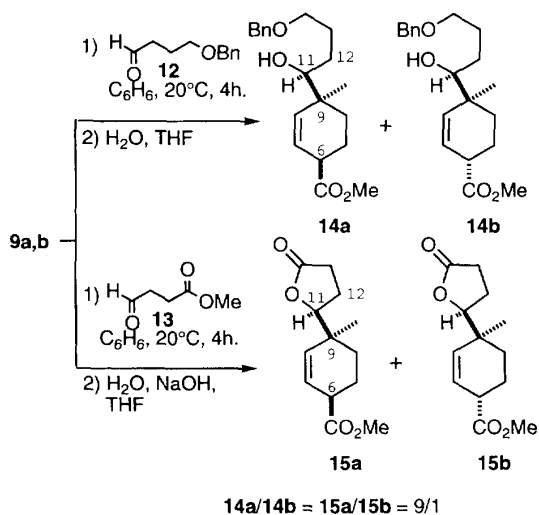
Scheme 5

15a,b in 63 and 67% yield respectively, from catecholborane (scheme 6).

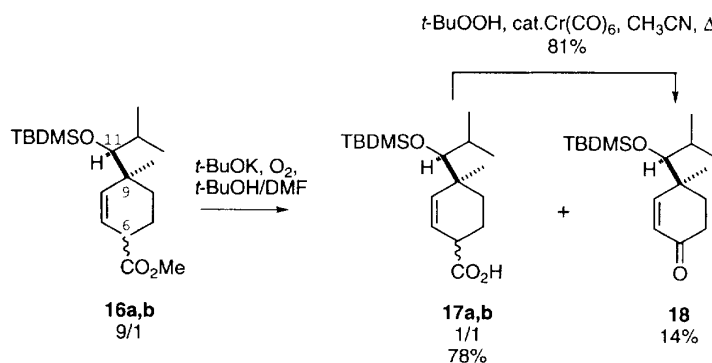
Oxidative decarboxylation

An oxidative decarboxylation at carbon 6 was used in order to prepare the model compounds **3**. Silylated derivatives **16a,b** were obtained by treatment of alcohols **10a,b** with Corey's silylating reagent (TBDMSTf, 2,6-lutidine, CH_2Cl_2 94% yield). They were treated with various oxidation reagents: $\text{SeO}_2/t\text{-BuOOH}$ [6], $\text{Na}_2\text{WO}_4/\text{NaOH}/\text{H}_2\text{O}_2$ [7], NBS/ $(n\text{-Bu}_4\text{N})_2\text{Cr}_2\text{O}_7$ [8], $\text{Na}_2\text{Cr}_2\text{O}_7/\text{AcOH}/\text{Ac}_2\text{O}$ [9], PCC [10] and $\text{CrO}_3/t\text{-BuOOH}$ [11]. Enone **18** was obtained in low yield, and proved to be very sensitive to acidic media as well as to most of the oxidative decarboxylation reagents. A milder two-step procedure was then studied.

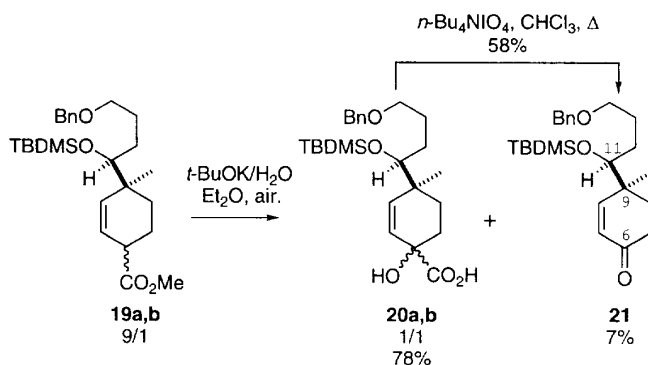
Treatment of **16a,b** with $t\text{-BuOK}/t\text{-BuOH}$ in anhydrous DMF under a gentle flow of oxygen afforded 78% of a 1:1 mixture of acids **17a,b** along with 14% of enone **18** presumably formed via in-situ-generated dioxetanone [12]. Compound **18** decomposes slowly and so the best yields were obtained when this reaction was quenched after 18 h, and when the mixture of acids then underwent an oxidative decarboxylation promoted by $t\text{-BuOOH}$ in the presence of a catalytic amount of $\text{Cr}(\text{CO})_6$ [13]. The enone **18** was then obtained with 77% overall yield from **16a,b** (scheme 7).



Scheme 6



Scheme 7



Scheme 8

A similar sequence with **19a,b**, which was obtained by silylation of **14a,b**, gave only poor yields of enone **21**. This enone was eventually obtained with 52% overall yield via a slightly different reaction pathway. When it was treated with $t\text{-BuOK}$ in the presence of air (not dried), **19a,b** afforded 78% of a 1:1 mixture of α -hydroxyacids **20a,b** along with 7% of enone **21**. The oxidative decarboxylation of the intermediate α -hydroxyacids was carried out with tetrabutylammonium periodate ($n\text{-Bu}_4\text{NIO}_4$) (scheme 8) [14].

Conclusion

We have shown that a model compound such as **3** bearing reactive groups that allow the construction of both the *trans*-decalinic and the furofuranic moieties of clerodin and with the appropriate stereochemistry at carbons C_9 and C_{11} can be easily obtained via a two-step procedure involving a Diels–Alder cycloaddition of a 1,3-dienylboronate to an activated dienophile, followed by the condensation of an aldehyde on the resulting allylic boronate. Oxidative decarboxylation of the resulting methyl ester afforded the desired enone **3**. The use of a chiral boronate as well as a Michael addition to this enone to form the decalinic backbone of clerodin are currently under study. The introduction of the methyl at C_8 has been investigated in our laboratory and can be achieved subsequently through a

previously described selenation/oxidation/Michael addition sequence taking advantage of the ketone at C_6 [2]. Diels–Alder reactions with other dienophiles will be reported in due course.

Experimental section

General

NMR spectra were recorded in CDCl_3 solutions using Bruker WP 200 (^1H at 200 MHz, ^{13}C at 50.1 MHz) or AM 400 spectrometers (^1H at 400 MHz, ^{11}B at 128.3 MHz and ^{13}C at 100.3 MHz). ^1H NMR spectra were referenced to internal tetramethylsilane, ^{13}C NMR to CDCl_3 (reference $\delta = 77.14$), and ^{11}B to external $\text{BF}_3 \cdot \text{OEt}_2$ solution ($\delta = 0$). Column chromatography was performed with silica gel 60 (230–400 mesh, Merck). All reactions were performed under a nitrogen atmosphere unless indicated otherwise. Anhydrous THF, Et_2O , pentane and benzene were distilled from sodium/benzophenone; DMF was distilled under reduced pressure (15 mmHg) from CaH_2 ; and CH_3CN was distilled from P_2O_5 . Catecholborane was purchased from Lancaster, and enyne **7** was prepared as described previously [15] and kept over $\text{MgSO}_4/\text{Na}_2\text{CO}_3$ (1:1). Aldehyde (**12**) was prepared in 90% yield from butane-1,4-diol by a monobenzoylation/oxidation (PDC) procedure. Aldehyde (**13**) was prepared from commercially available 3-(methoxycarbonyl)propanoyl chloride by a reductive hydrogenation [16].

Methyl 4-(1-hydroxy-2-methylpropyl)-4-methylcyclohex-2-ene-1-carboxylate 10a,b

To a cooled (0 °C) solution of enyne **7** (2 g, 30 mmol) was added dropwise catecholborane (2.15 mL, 20 mmol). The solution was then heated and stirred for 2 h at 60 °C, with an efficient dry ice condenser to prevent excessive loss of **7**. The slurry was then cooled to room temperature and triturated with pentane (5 mL). Excess catecholborane precipitated. The pentane extract was filtered, evaporated and pure **8** (3.27 g, 88% yield) was recovered as white needles (¹¹B NMR: δ = 31.7).

Diene **8** was then dissolved in methyl acrylate (7.2 mL, 80 mmol) and the mixture was heated to 79 °C and stirred for 12 h. The yellow slurry was then cooled to room temperature, excess methyl acrylate was evaporated, and NMR analysis of an analytical sample revealed the presence of the two isomers **9a,b** in a 9:1 ratio.

The slurry was then dissolved in anhydrous benzene (50 mL), and freshly redistilled isobutyraldehyde was added (4 mL, 45 mmol). The solution was stirred for 12 h at room temperature. The solvent was evaporated, the residue was dissolved in a 9:1 THF/H₂O solution (50 mL), and was refluxed for 4 h. The solution was then dissolved in Et₂O (300 mL), and water (10 mL) was added. The aqueous phase was extracted with Et₂O (3 × 50 mL), the organic phases were combined, dried over MgSO₄, and the solvents were evaporated. The resulting material was chromatographed on silica gel using Et₂O/pentane (10:90 then 20:80 and 30:70) for the elution to give 3.4 g (76%) of a 9:1 mixture of isomers **10a,b** as a pale yellow oil.

• *Major isomer 10a*

IR (neat): 3 531, 2 956, 2 871, 1 734, 1 450, 1 198.

¹H NMR (400 MHz) δ : 5.77 (1H, dd, J = 4.5, 10 Hz), 5.61 (1H, dd, J = 2, 10 Hz), 3.66 (3H, s), 3.21 (1H, d, J = 2.5 Hz), 3.01 (1H, qd, J = 4.5, 2 Hz), 1.9–2 (3H, m), 1.80 (1H, m), 1.67 (1H, broad s), 1.27 (1H, m), 0.99 (3H, s), 0.97 and 0.89 (3H and 3H, 2d, J = 7 Hz).

¹³C NMR (50.1 MHz) δ : 174.5, 137.3, 124.5, 81.6, 51.9, 40.5, 28.8, 28.7, 27.0, 24.3, 23.4, 22.0 and 16.7.

Anal calc for C₁₃H₂₂O₃: C, 69.0; H, 9.8. Found: C, 69.14; H, 10.03.

• *Minor isomer 10b*

¹H NMR (400 MHz) δ : 5.81 (1H, dd, J = 3, 9 Hz), 5.61 (1H, dd, J = 3, 9 Hz), 3.71 (3H, s), 3.18 (1H, d, J = 2 Hz), 3.01 (1H, m), 1.45 (1H, m), 1.04 (3H, s), 0.97 and 0.89 (3H and 3H, 2d, J = 7 Hz).

¹³C NMR (50.1 MHz) δ : 174.6, 136.3, 125.1, 82.2, 51.9, 42.7, 28.9, 28.7, 27.0, 24.3, 23.4, 22.0 and 16.7.

7-Isopropyl-1-methyl-6-oxabicyclo[3.2.1]octane-4-carboxylic acid 11

To a solution of the mixture of cyclohexenes **10a,b** (8.26 g, 36.5 mmol), in diethyl ether (250 mL) were successively added at 0 °C *t*-BuOK (21.5 g, 192 mmol) and water (0.88 mL, 48.6 mmol). The suspension was stirred for 12 h at room temperature. Hydrochloric acid solution (1N) was then added dropwise until the pH of the solution reached 2. The aqueous phase was then extracted with Et₂O (4 × 20 mL), and the combined organic phases were dried on MgSO₄. The crude product was washed with a cold solution of pentane, and **11** was collected as colorless needles (6.65 g, 86%): mp 80–82 °C.

IR (neat): 3 500–3 000 broad, 2 960, 2 872, 1 707, 1 051.

¹H NMR (200 MHz) δ : 9.6 (1H, broad s), 4.58 (1H, d, J = 6.5 Hz), 3.18 (1H, d, J = 10 Hz), 2.36 (1H, dd, J = 6, 11.5 Hz), 2.0–2.15 (3H, m), 1.75–1.85 (2H, m), 1.46 (1H, d, J = 11.5 Hz), 1.35–1.45 (1H, m), 1.07 (3H, s), 1.03 and 0.89 (3H and 3H, 2d, J = 6.5 Hz).

¹³C NMR (50.1 MHz) δ : 178.9, 93.1, 74.5, 47.6, 46.7, 40.6, 32.0, 28.3, 24.1, 21.9, 21.2 and 19.6.

MS (EI): 43, 55, 67, 79, **94**, 122, 140, 169, 212 (M⁺).

Anal calc for C₁₂H₂₀O₃: C, 67.89; H, 9.5. Found: C, 67.64; H, 9.53.

Methyl 4-(4-benzoyloxy-1-hydroxybutyl)-4-methylcyclohex-2-ene-1-carboxylate 14a,b

This was prepared following the procedure employed for **10a,b** with 2.1 mmol of catecholborane and aldehyde **12**. A 9:1 mixture of isomers **14a,b** was recovered as a colorless oil (0.44 g, 63%).

• *Major isomer 14a*

¹H NMR (200 MHz) δ : 7.21 (5H, broad s), 5.72 (1H, dd, J = 4, 10 Hz), 5.50 (1H, dd, J = 1.5, 10 Hz), 4.43 (2H, s), 3.64 (3H, s), 3.42 (2H, t, J = 6 Hz), 3.27 (1H, broad d, J = 10 Hz), 2.96 (1H, m), 2.7 (1H, broad s), 1.5–2 (8H, m), 0.89 (3H, s).

¹³C NMR (50.1 MHz) δ : 174.5, 139.4, 138.4, 128.3 (2C), 127.7 (2C), 127.5, 124.0, 77.0, 72.9, 70.4, 51.8, 40.8, 30.0, 29.4, 28.4, 27.4, 23.4 and 22.2.

• *Minor isomer 14b*

¹H NMR (200 MHz) δ : 7.35 (5H, broad s), 5.90 (1H, dd, J = 4, 10 Hz), 5.45 (1H, dd, J = 1.5, 10 Hz), 4.43 (2H, s), 3.7 (3H, s), 3.55 (2H, t, J = 7 Hz), 3.35 (1H, broad d, J = 8 Hz), 3.05 (1H, m), 2.7 (1H, broad s), 1.2–2.1 (8H, m), 1.0 (3H, s).

Methyl 4-methyl-4-(5-oxo-tetrahydrofuran-2-yl)cyclohex-2-ene-1-carboxylate 15a,b

This was prepared following the procedure employed for **10a,b** with 6.6 mmol of catecholborane and aldehyde **13**. Final hydrolysis was realized with 0.1 M NaOH instead of H₂O. The 9:1 mixture of isomers **15a,b** was recovered as a colorless oil (1.06 g, 67%).

• *Major isomer 15a*

IR (neat): 2 953, 1 771, 1 735, 1 497, 1 460, 1 437, 1 342, 1 266, 1 394.

¹H NMR (400 MHz) δ : 5.85 (1H, dd, J = 4, 10 Hz), 5.53 (1H, dd, J = 2, 10 Hz), 4.30 (1H, dd, J = 7, 9 Hz), 3.66 (3H, s), 3.04 (1H, m), 2.46–2.51 (2H, m), 2.1–2.2 (1H, m), 1.9–2.1 (2H, m), 1.8–1.9 (1H, m), 1.75 (1H, tt, J = 3.5, 10 Hz), 1.37 (1H, ddd, J = 3.5, 7.5, 14 Hz), 1.06 (3H, s).

¹³C NMR (100.3 MHz) δ : 177.1, 175.4, 132.3, 126.5, 85.8, 51.9, 40.5, 38.0, 29.5, 29.0, 23.3, 22.7, 21.0.

MS (IE): 29, 79, 85, **93**, 153, 238 (M⁺).

HRMS calc: 238.1205, found: 238.1205.

• *Minor isomer 15b*

¹H NMR (400 MHz) δ : 5.86 (1H, dd, J = 3, 10 Hz), 5.51 (1H, dd, J = 2, 10 Hz), 4.25 (1H, dd, J = 7, 9 Hz), 3.68 (3H, s), 3.04 (1H, m), 2.46–2.51 (2H, m), 2.1–2.2 (1H, m), 1.9–2.1 (2H, m), 1.8–1.9 (1H, m), 1.75 (1H, m), 1.37 (1H, m), 1.02 (3H, s).

¹³C NMR (50.1 MHz) δ : 177.1, 175.6, 132.4, 127.2, 86.5, 52.3, 41.6, 38.3, 29.6, 29.0, 23.1, 22.7, 21.5.

Methyl 4-{1-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}cyclohex-2-ene-1-carboxylate 16a,b

To a cooled (0 °C) solution of 2,6-lutidine (5.3 mL, 45.2 mmol) in CH₂Cl₂ (10 mL) were added successively a mixture of **10a,b** (4.1 g, 18.1 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (5 mL, 21.8 mmol). The solution was left for 1 h at 0 °C and then allowed to reach room temperature. The solution was then diluted with CH₂Cl₂ (100 mL), and washed successively with water (5 mL), a 0.1 N solution of hydrochloric acid (5 mL) and brine (5 mL). The organic phase was then dried over MgSO₄, and the solvents were evaporated. The resulting material was chromatographed on silica gel using AcOEt/cyclohexane (5:95) for the elution to afford 5.8 g of the 9:1 mixture of isomers **16a,b** as a colorless oil.

• *Major isomer 16a*

IR (neat): 2955, 2930, 2856, 1741, 1471, 1463, 1252, 1056.

¹H NMR (200 MHz) δ: 5.67 (2H, m), 3.69 (3H, s), 3.29 (1H, t, *J* = 3 Hz), 3.01 (1H, m), 1.7–2.0 (4H, m), 1.27 (1H, m), 0.97 (3H, s), 0.92 (9H, s), 0.89 (3H, d, *J* = 6 Hz), 0.85 (3H, d, *J* = 6 Hz), 0.07 and 0.06 (3H and 3H, 2s).

¹³C NMR (50.1 MHz) δ: 174.5, 137.7, 123.2, 82.5, 51.8, 40.7 (2C), 29.9, 29.1, 26.5 (3C), 24.4, 24.2, 21.5, 18.4, 17.5, –2.9 and –3.7.

Anal calc for C₁₉H₃₆O₃Si: C, 67.00; H, 10.65. Found: C, 67.3; H, 10.2.

• *Minor isomer 16b*

¹H NMR (200 MHz) δ: 5.70 (1H, dd, *J* = 3, 9 Hz), 5.59 (1H, dd, *J* = 2, 9 Hz), 3.70 (3H, s), 3.23 (1H, t, *J* = 3 Hz), 3.01 (1H, m), 1.7–2.0 (4H, m), 1.27 (1H, m), 0.96 (3H, s), 0.92 (9H, s), 0.89 (3H, d, *J* = 6 Hz), 0.85 (3H, d, *J* = 6 Hz), 0.08 and 0.06 (3H and 3H, 2s).

¹³C NMR (50.1 MHz) δ: 174.5, 137.9, 123.6, 83.4, 51.8, 41.8, 40.7, 29.6, 29.0, 26.8 (3C), 24.5, 24.2, 22.5, 18.8, 17.5, –2.9 and –3.7.

4-{1-[(tert-Butyldimethylsilyl)oxy]-2-methylpropyl}-4-methylcyclohex-2-en-1-one 18

In a flask equipped with a gas inlet, were introduced successively freshly distilled DMF (5 mL), *t*-BuOH (10 mL), *t*-BuOK (0.11 g, 0.98 mmol), *n*-Bu₄NI (0.008 g, 0.023 mmol) and the 9:1 mixture of protected alcohols **16a,b** (0.16 g, 0.46 mmol), prepared in 94% yield from alcohols **10a,b** with the same procedure used for **19a,b**, vide infra. Oxygen was then slowly bubbled through this mixture for 3 days. The solution was then diluted with CH₂Cl₂ (50 mL) and slowly acidified to pH 3 with a 0.1 N solution of hydrochloric acid. The aqueous phase was then extracted with CH₂Cl₂ (3 × 20 mL), the organic phases were gathered and dried over Na₂SO₄. Solvents were evaporated, and chromatography on silica gel using AcOEt/cyclohexane (30:70) and then AcOEt/AcOH (98:2) for the elution yielded 0.020 g (14%) of enone **18** and 0.120 g (78%) of the 1:1 mixture of acids **17a,b**.

• *Isomer 17a*

IR (in CHCl₃): 3500–2500, 2957, 2929, 2857, 1707, 1252, 1054.

¹H NMR (200 MHz) δ: 8.7 (1H, broad s), 5.73 (2H, s), 3.31 (1H, d, *J* = 2 Hz), 3.07 (1H, td, *J* = 5.5, 2 Hz), 1.82–2.01 (4H, m), 1.17–1.29 (1H, m), 0.98 (3H, s), 0.93 (9H, s), 0.94 and 0.90 (3H and 3H, 2d, *J* = 6.5 Hz), 0.09 and 0.07 (3H and 3H, 2s).

¹³C NMR (50.1 MHz) δ: 179.9, 138.2, 122.7, 82.6, 40.9, 40.7, 29.9, 29.4, 26.5, 24.2, 24.1, 21.4, 18.9, 17.6, –2.9 and –3.6.

• *Isomer 17b*

¹H NMR (200 MHz) δ: 8.7 (1H, broad s), 5.70 (1H, dd, *J* = 2, 8 Hz), 5.50 (1H, dd, *J* = 1.5, 8 Hz), 3.25 (1H, d, *J* = 2 Hz), 3.00–3.10 (1H, m), 1.75–2.04 (4H, m), 1.2–1.3 (1H, m), 1.00 (3H, s), 0.92 (9H, s), 0.94 and 0.89 (3H and 3H, 2d, *J* = 6.5 Hz), 0.09 and 0.07 (3H and 3H, 2s).

¹³C NMR (50.1 MHz) δ: 180.9, 138.3, 123.0, 83.5, 41.6, 41.5, 29.7, 29.2, 26.5, 24.4, 24.2, 22.4, 18.9, 17.7, –2.9 and –3.5.

The mixture of acids **17a,b** was then dissolved in freshly distilled CH₃CN (15 mL). To the mixture Cr(CO)₆ (20 mg, 0.09 mmol) and *t*-BuOOH (0.5 mL of a 3 M solution in toluene) were added. The solution was refluxed for 14 h, cooled to room temperature, CH₃CN evaporated under reduced pressure and the pale green crude material was diluted with pentane (1 mL) and filtered over neutral Al₂O₃ using pentane for the elution. Enone **18** was recovered in 81% yield (altogether 77% yield from **16a,b**) as a pale colorless oil. The enone proved to be very sensitive, and spontaneously slowly decomposed even when kept at 0 °C.

IR (neat): 2957, 2930, 2856, 1684, 1464, 1388, 1256, 1111, 1056.

¹H NMR (200 MHz) δ: 6.63 (1H, dd, *J* = 1.5, 10.5 Hz), 5.90 (1H, d, *J* = 10.5 Hz), 3.42 (1H, d, *J* = 2 Hz), 2.51 (1H, dd, *J* = 1.5, 5 Hz), 2.46 (1H, d, *J* = 5 Hz), 2.20 (1H, dd, *J* = 2, 13 Hz), 1.96 (1H, hept d, *J* = 7, 2 Hz), 1.68 (1H, dtd, *J* = 1.5, 5, 13 Hz), 1.15 (3H, s), 0.94 (9H, s), 0.99 and 0.89 (3H and 3H, 2d, *J* = 7 Hz), 0.12 and 0.08 (3H and 3H, 2s).

¹³C NMR (50.1 MHz) δ: 199.3, 158.0, 128.3, 82.9, 42.7, 34.3, 30.7, 29.8, 26.5 (3C), 23.7, 22.8, 18.9, 17.4, –2.9 and –3.6.

Methyl 4-{4-benzyloxy-1-[(tert-butyldimethylsilyl)oxy]-butyl}-4-methylcyclohex-2-ene-1-carboxylate 19a,b

To a cooled (0 °C) solution of 2,6-lutidine (0.34 mL, 2.9 mmol) in CH₂Cl₂ (2 mL) were added successively a mixture of **14a,b** (0.39 g, 1.2 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.4 mL, 1.8 mmol). The solution was left for 1 h at 0 °C and then allowed to reach room temperature. The solution was then diluted with CH₂Cl₂ (100 mL), and washed successively with water (5 mL), a 0.1 N solution of hydrochloric acid (5 mL) and brine (5 mL). The organic phase was then dried over MgSO₄, and the solvents were evaporated. The resulting material was chromatographed on silica gel using AcOEt/cyclohexane (5:95) for the elution to afford 0.465 g of the 9:1 mixture of isomers **19a,b** as a colorless oil.

• *Major isomer 19a*

IR (neat): 3028, 2953, 2929, 2855, 1737, 1474, 1461, 1454, 1361, 1256, 1094.

¹H NMR (400 MHz) δ: 7.29–7.37 (5H, m), 5.74 (1H, dd, *J* = 3.5, 10.5 Hz), 5.62 (1H, dd, *J* = 2, 10.5 Hz), 3.68 (3H, s), 3.52 (1H, t, *J* = 6 Hz), 3.51 (1H, m), 3.01–3.06 (1H, m), 1.2–2.0 (4H, m), 1.27 (1H, m), 0.98 (3H, s), 0.91 (9H, s), 0.07 and 0.06 (3H and 3H, 2s).

¹³C NMR (50.1 MHz) δ: 174.6, 139.3, 137.4, 128.4 (2C), 127.6 (2C), 127.5, 123.7, 78.0, 72.8, 70.6, 51.8, 40.9, 40.1, 29.9, 29.6, 27.6, 26.2 (3C), 23.3, 21.4, 18.4, –3.5 and –3.8.

MS (IE): **28**, 41, 55, 73, 187, 279, 369.

Anal calc for C₂₆H₄₂O₄Si: C, 69.91; H, 9.48. Found: C, 70.3; H, 9.12.

• **Minor isomer 19b**

¹H NMR (400 MHz) δ : 7.29–7.37 (5H, m), 5.70 (1H, dd, $J = 2, 10$ Hz), 5.58 (1H, dd, $J = 2, 10$ Hz), 3.71 (3H, s), 3.52 (1H, t, $J = 6$ Hz), 3.51 (1H, m), 3.01–3.06 (1H, m), 1.2–2.0 (4H, m), 1.27 (1H, m), 1.00 (3H, s), 0.93 (9H, s), 0.07 and 0.06 (3H and 3H, 2s).

4-{[4-Benzoyloxy-1-[(tert-butyldimethylsilyl)oxy]butyl]-4-methylcyclohex-2-en-1-one 21

To a solution of the 9:1 mixture of protected alcohols **19a,b** (0.4 g, 0.9 mmol) in Et₂O (5 mL) were added successively at 0 °C *t*-BuOK (0.8 g, 7.2 mmol) and water (0.032 mL, 1.8 mmol). The slurry was exposed to open air and stirred for 3 days at room temperature. The pale yellow slurry was then diluted with Et₂O (50 mL) and acidified with a dropwise addition of hydrochloric acid. The aqueous phases were extracted with Et₂O (3 × 20 mL), and the organic phases were dried over Na₂SO₄. Solvents were evaporated, and the crude material was chromatographed on silica gel using AcOEt/cyclohexane (30:70) and then AcOEt/AcOH (98:2) for the elution yielding 0.023 g (7%) of enone **22** and 0.316 g (78%) of the 1:1 mixture of α -hydroxy acids **20a,b** (white needles, mp = 157–158 °C).

• **Isomers 20a,b**

IR (in CHCl₃): 3 582, 3 000–3 500, 3 029, 2 955, 2 929, 2 857, 1 712, 1 471, 1 462, 1 362, 1 257, 1 091.

¹H NMR (400 MHz) δ : 7.31–7.37 (5H and 5H, m), 5.88 and 5.82 (1H and 1H, d, $J = 10$ Hz), 5.63 and 5.57 (1H and 1H, d, $J = 10$ Hz), 4.51 (2H and 2H, s), 3.45 (3H and 3H, m), 1.4–2.2 (8H and 8H, m), 1.03 and 1.02 (3H and 3H, s), 0.91 (9H and 9H, s), 0.08, 0.07, 0.04 and 0.03 (3H, 3H, 3H and 3H, s).

¹³C NMR (50.1 MHz) δ : 179.6 and 179.3, 140.2 (2C), 138.3 (2C), 128.5 (4C), 127.8 (4C), 128.6 (2C), 126.3 and 125.2, 78.7 and 77.8, 72.9 (2C), 72.1 and 71.7, 70.6 (2C), 40.8 and 40.3, 30.6 and 30.4, 30.0 (2C), 27.3 and 27.1, 26.8 (2C), 26.2 (6C), 23.0 and 22.6, 18.4 (2C), –3.6 (2C) and –3.8 (2C).

MS (EI): 32, 44, 73, **91**, 145, 209 (M⁺-OTBDMS and -OBn).

The mixture of acids **20a,b** was then diluted with CHCl₃ (5 mL), *n*-Bu₄NIO₄ (0.37 g, 8.5 mmol) was added and the solution was then refluxed for 10 h. The solvent was then evaporated under reduced pressure and flash chromatography on silica gel was performed using AcOEt/cyclohexane (30:70) for the elution yielding 0.165 g (58%) (altogether 52% yield from **19a,b**) of enone **21** as a yellow oil.

IR (neat): 2 957, 2 928, 2 855, 1 672, 1 462, 1 389, 1 258, 1 096.

¹H NMR (400 MHz) δ : 7.31–7.37 (5H, m), 6.78 (1H, dd, $J = 1, 10$ Hz), 5.90 (1H, d, $J = 10$ Hz), 4.54 (2H, s), 3.56 (1H, dd, $J = 3, 7$ Hz), 3.43 (2H, td, $J = 6, 2$ Hz), 2.47

(1H, dd, $J = 5.5, 8$ Hz), 2.18 (1H, dt, $J = 16.5, 8$ Hz), 1.43–1.80 (6H, m), 1.14 (3H), 0.88 (9H, s), 0.08 and 0.05 (3H and 3H, 2s).

¹³C NMR (50.1 MHz) δ : 199.6, 158.0, 138.7, 128.5 (2C), 128.4, 127.7 (2C), 127.6, 78.2, 73.0, 70.5, 41.9, 34.1, 30.3, 30.0, 27.0, 26.2 (3C), 22.1, 18.4, –3.5, –3.8.

MS (EI): 59, 73, 91, 145, 165, 187, 345 (M⁺-*t*-Bu).

References and notes

- a) Van Beek TA, de Groot Ae, *Recl Trav Chim Pays-Bas* (1986) 105, 513
b) de Groot Ae, Van Beek TA, *ibid* (1987) 106, 1
c) Meritt AT, Ley SV, *Nat Prod Reports* (1992) 243.
- a) Bouchard H, Lallemand JY, *Tetrahedron Lett* (1990) 31, 5151
b) Bouchard H, Soulié J, Lallemand JY, *Tetrahedron Lett* (1991) 32, 5957.
- Bouchard H, Renard PY, Lallemand JY, *Tetrahedron Lett* (1991) 32, 5953.
- a) Vaultier M, Truchet F, Carboni B, Hoffmann RW, Denne I, *Tetrahedron Lett* (1987) 28, 4169
b) Wang X, *J Chem Soc, Chem Commun* (1991) 1515.
- Gassman PG, Schenk WN, *J Org Chem* (1977) 42, 918.
- a) Trachtenberg EN, Carver JR, *J Org Chem* (1970) 35, 1646
b) Haruna M, Ito K, *J Chem Soc, Chem Commun* (1981) 483
c) Umbreit MA, Sharpless KB, *J Am Chem Soc* (1977) 99, 5526.
- Toro A, Ambrus G, *Tetrahedron Lett* (1990) 31, 3475.
- a) Landini D, Rolla F, *Chem & Ind* (1979) 213
b) Santaniello E, Ferraboschi P, *Synth Commun* (1980) 75.
- Marshall JA, Cohen GM, *J Org Chem* (1971) 36, 877.
- Parish EJ, Wei TY, *Synth Commun* (1987) 17, 1227.
- Muzart J, *Tetrahedron Lett* (1987) 28, 2131, 2133 and 4665.
- Heckmann B, Alayrac C, Mioskowski C, Chandrasekhar S, Falck JR, *Tetrahedron Lett* (1992) 33, 5205.
- a) Pearson AJ, Han GR, *J Org Chem* (1985) 50, 2791
b) Pearson AJ, Chen YS, Han GR, Hsu SY, Ray T, *J Chem Soc, Perkin Trans I* (1985) 267.
- Santaniello E, Manzocchi A, Farachi C, *Synthesis* (1980) 563.
- Brandsma L, *Preparative Acetylenic Chemistry*, Elsevier, Amsterdam, 1971.
- Holmes AB, Tabor AB, Baker R, *J Chem Soc, Chem Commun* (1991) 3301.